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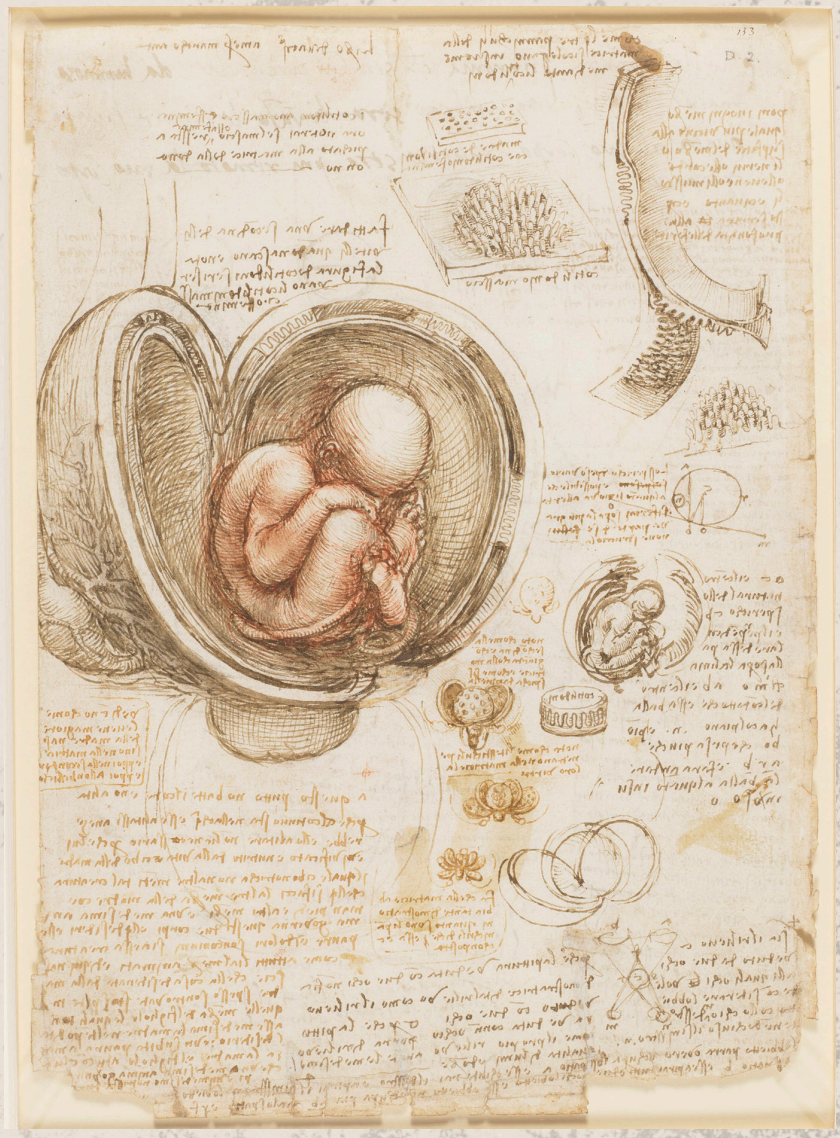
HEALTH IN TRANSITION

Translating developmental origins of health and disease science to improve future health in Africa



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HYPERGLYCAEMIA IN PREGNANCY

Eugene Sobngwi[1]

According to the International Diabetes Federation, the burden of diabetes is progressively rising worldwide with an expected doubling of prevalence in most low- and middle-income settings within twenty-five years. The projected surge in diabetes prevalence to epidemic proportions reflects the ongoing so-called epidemiological transition experienced across most of the fastest-growing economies. The concept of epidemiological transition is characterised by the reduction in infectious disease burden and a quasi-parallel rise in chronic non-communicable disease burden as the result of better health care, reduced fertility, lifestyle changes, increased life expectancy and changing age structure of populations.

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The specificity of epidemiological transition in most African nations is its accelerated character compared to most Western countries where the transition took place over two to three centuries. As a result, chronic non-communicable diseases frequently occur at a lower age than previously reported, including in women of childbearing age.

This chapter reviews key knowledge about the pathophysiology and consequences of hyperglycaemia in pregnancy, and their implication for screening, diagnosis and management strategy in high risk but resource-limited populations, with special emphasis on Africa.

Introduction

Hyperglycaemia in pregnancy has adverse consequences for the mother, the outcome of pregnancy, and her offspring, in turn creating challenges for care providers and the healthcare system. Underdiagnosis, and the resulting absence and sub-optimal management further increase the related burden. In developmental origins of health and disease (DOHaD) perspective, hyperglycaemia in pregnancy is an issue of major importance because it is frequent, often asymptomatic and undiagnosed, has a proven impact on the fetus and the infant after birth, and its effects then extend into adult age. Changes in the internationally accepted diagnostic criteria and strategies for management have raised concern and recognised the need for clarification. Despite the scarcity of population-based data from the most affected parts of the world, there is growing evidence from Africa to suggest a rise in early-onset diabetes and hyperglycaemia in pregnancy.

Despite progress in maternal and child health globally, adverse pregnancy outcomes remain unacceptably high in most sub-Saharan African countries, where they are mainly due to preventable causes.[2] One of those preventable causes, gestational diabetes, disproportionately affects women of African ethnicity.[3] Diabetes mellitus

2 Lawn, J.E., Blencowe, H., Pattinson, R., Cousen, S., Kumar, R., Ibiebele, I., Gardosi, J., Day, L.T., Stanton, C. & Lancet's Stillbirths Series Steering Committee. 2011. Stillbirths: Where? When? Why? How to make the data count? *The Lancet*, 377(9775):1448-1463. [https://doi.org/10.1016/S0140-6736(10)62187-3]; Pattinson, R., Kerber, K., Buchmann, E., Friberg, I.K., Belizan, M., Lansky, S., Weissman, E., Mathai, M., Rudan, I., Walker, N., Lawn, J.E. & Lancet's Stillbirths Series Steering Committee. 2011. Stillbirths: how can health systems deliver for mothers and babies? *The Lancet*, 377(9777):1610-1623. [https://doi.org/10.1016/S0140-6736(10)62306-9].

3 Makgoba, M., Savvidou, M.D. & Steer, P.J. 2012. An analysis of the interrelationship between maternal age, body mass index and racial origin in the development of gestational diabetes mellitus. *BJOG: An International Journal of Obstetrics & Gynaecology*, 119(3):276-282. [https://doi.org/10.1111/j.1471-0528.2011.03156.x].

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has been associated with up to eight per cent of stillbirths in developed countries against less than two per cent in other parts of the world.[4] However, the latter figures are likely underestimated, as the true magnitude of gestational diabetes remains unknown in most low- to-middle income countries, including those in Africa.[5] In the absence of effective and universal screening programmes, current figures suggest that close to 90 per cent of cases of gestational diabetes occur in low- to-middle income countries including Africa while less than 10 per cent of African woman undergo screening for diabetes during pregnancy.[6]

Detecting and treating gestational diabetes provides benefits in terms of reducing fetal morbidity and mortality, as well as the future maternal risk of developing type 2 diabetes mellitus.[7] However, optimal strategies for gestational diabetes diagnosis remain elusive.[8] Different diagnostic criteria have been proposed by different professional bodies and organisations. Recently the International Association of Diabetes and Pregnancy Study Group suggested new diagnostic criteria, informed mainly by the Hyperglycaemia and Adverse Pregnancy Outcome study. However,

4 Lawn et al., 2011; Cousens, S., Blencowe, H., Stanton, C., Chou, D., Ahmed, S., Steinhardt, L., Creanga, A.A., Tunçalp, O., Balsara, Z.P., Gupta, S., Say, L. & Lawn, J.E. 2011. National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis. *The Lancet*, 377(9774):1319-1330. [https://doi.org/10.1016/S0140-6736(10)62310-0].

5 Jiwani, A., Marseille, E., Lohse, N., Damm, P., Hod, M. & Kahn, J.G. 2012. Gestational diabetes mellitus: results from a survey of country prevalence and practices. *Journal of Maternal-Fetal and Neonatal Medicine*, 25(6):600-610. [https://doi.org/10.3109/14767058.2011.587921].

6 International Diabetes Federation (IDF). 2015. *IDF Diabetes Atlas 7th Edition* (2015). [https://www.idf.org/component/attachments/attachments.html?id=1093&task=download] (Accessed 24 August 2016); Mwanri, A.W., Kinabo, J., Ramaiya, K. & Feskens, E.J. 2015. Gestational diabetes mellitus in sub-Saharan Africa: systematic review and metaregression on prevalence and risk factors. *Tropical Medicine & International Health*, 20(8):983-1002. [https://doi.org/10.1111/tmi.12521].

7 Lohse, N., Marseille, E. & Kahn, J.G. 2011. Development of a model to assess the cost-effectiveness of gestational diabetes mellitus screening and lifestyle change for the prevention of type 2 diabetes mellitus. *International Journal of Gynecology & Obstetrics*, 115(Supplement 1):20-25. [https://doi.org/10.1016/S0020-7292(11)60007-6]; Ohno, M.S., Sparks, T.N., Cheng, Y.W. & Caughey, A.B. 2011. Treating mild gestational diabetes mellitus: a cost-effectiveness analysis. *American Journal of Obstetrics and Gynecology*, 205(3):282.e1-7. [https://doi.org/10.1016/j.ajog.2011.06.051].

8 Simmons, D., McElduff, A., McIntyre H.D. & Elrishi, M. 2010. Gestational Diabetes Mellitus: NICE for the U.S.? A Comparison of the American Diabetes Association and the American College of Obstetricians and Gynecologists Guidelines With the U.K. National Institute for Health and Clinical Excellence Guidelines: Response to Holt et al. *Diabetes Care*, 33:34-37. [https://doi.org/10.2337/dc09-2335].

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even these new criteria are somewhat arbitrary, as this study identified continuous associations between maternal glucose levels and several perinatal outcomes, extending the threshold for a gestational diabetes diagnosis.[9]

Because of their high risk of diabetes, women of African ethnicity are offered universal screening for gestational diabetes in most developed countries. Such universal screening is not often available in developing countries because of poor financial and health care resources, and competing health priorities. Adequate approaches should account for the overall population risk and coping capacity of the health systems. Awareness of risk factors such as a family history of diabetes is as low as 30 per cent in most sub-Saharan Africa settings.[10] Moreover, diagnosing gestational diabetes requires the resource- and labour-intensive oral glucose tolerance test, seldom performed in African settings due to many constraints.[11] Consequently, gestational diabetes is either not screened for at all or is screened using inaccurate tests such as urine glucose.

Drivers of the risk of hyperglycaemia in pregnancy

Classification and considerations

Hyperglycaemia and hypertension are among the most common medical conditions encountered during pregnancy; estimates are that one in six live births occur in a context of maternal hyperglycaemia in pregnancy. However, because of greater prevalence of maternal and fetal complications resulting from diabetes mellitus antedating pregnancy, the International Federation of Obstetrics and Gynaecology has recommended that hyperglycaemia first detected at any time during pregnancy should be classified as either diabetes mellitus in pregnancy or gestational diabetes mellitus to account for this important fact and etiopathogenesis.

Maternal hyperglycaemia in pregnancy may thus be either due to pre-existing diabetes (type 1 or type 2) antedating pregnancy (estimated to be approximately 16 per cent of cases), or diabetes diagnosed for the first time in pregnancy where

9 Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group, Metzger, B.E., Lowe, L.P., Dyer, A.R., Trimble, E.R., Chaovarindr, U., Coustan, D.R., Hadden, D.R., McCance, D.R., Hod, M., McIntyre, H.D., Oats, J.J., Persson, B., Rogers, M.S., Sacks, D.A. 2008. Hyperglycemia and adverse pregnancy outcomes. *The New England Journal of Medicine*, 358(19):1991-2002. [https://doi.org/10.1056/NEJMoa0707943].

10 Mbanya, J.C., Motala, A.A., Sobngwi, E., Assah, F.K. & Enoru, S.T. 2010. Diabetes in sub-Saharan Africa. *The Lancet*, 375:2254-2266. [https://doi.org/10.1016/S0140-6736(10)60550-8].

11 Jiwani et al., 2012.

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studies meet the World Health Organization (WHO) criterion for diabetes mellitus in the non-pregnant state or due to gestational diabetes. The most commonly accepted definition of gestational diabetes is 'any degree of glucose intolerance with onset or first recognition during pregnancy'.[12] Compared to gestational diabetes, diabetes mellitus antedating pregnancy is more likely to be detected early (e.g. during the first trimester), provided appropriate testing is undertaken. While gestational diabetes is generally evident later in the course of pregnancy (often 24-28 weeks), it is diagnosed at any time when glucose levels meet the WHO criterion for the diagnosis of gestational diabetes (see Figure 9.1).

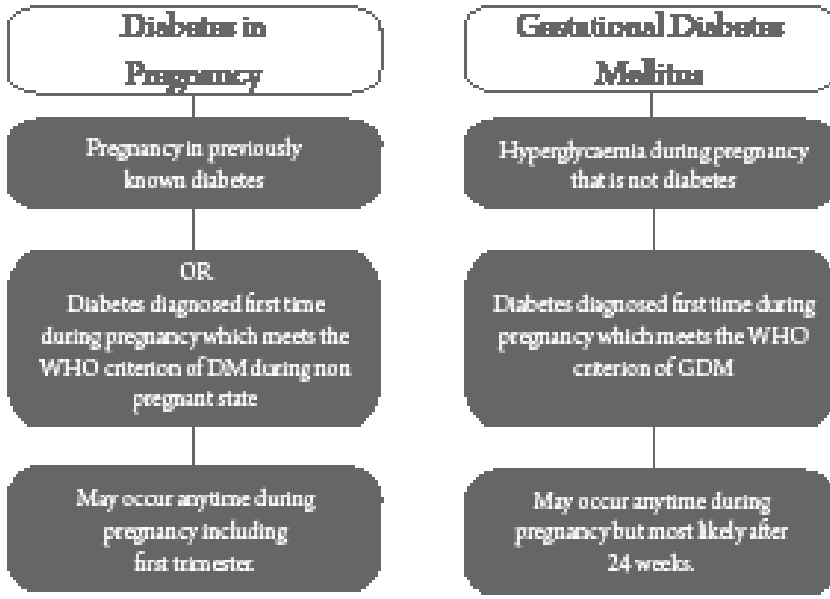

Figure 9.1 Schematic for the distinction between diabetes in pregnancy and gestational diabetes mellitus.

The role of classic factors

Due to shared risk factors, the occurrence of gestational diabetes parallels the prevalence of impaired glucose tolerance, obesity and type 2 diabetes in a given population. Worldwide, overweight and obesity are increasing in women of reproductive age, and the age of onset of diabetes is declining while the age of childbearing is increasing. Thus, in addition to family/genetic predisposition, increasing age combined with sedentary behaviour coupled with an unhealthy diet

12 American Diabetes Association. 2003. Gestational Diabetes Mellitus. *Diabetes Care*, 26(Supplement 1): 103-105. [https://doi.org/10.2337/diacare.26.2007.S103].

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and the resulting obesity, indicating more women entering pregnancy having risk factors that make them vulnerable to hyperglycaemia during pregnancy.

Other factors

Previous gestational diabetes is associated with a seven-fold lifetime risk of developing persistent type 2 diabetes. In the context of low diabetes awareness, unrecognised diabetes is, therefore, a potential additional factor. The other risk factors for gestational diabetes include ethnicity, high parity, excessive weight gain in the index pregnancy, polycystic ovarian syndrome, a history of poor pregnancy outcome (abortion, fetal loss), macrosomia in previous and/or index pregnancy, gestational diabetes in a previous pregnancy, preeclampsia and multi-fetal pregnancy.[13]

The second half of pregnancy is a diabetogenic state

Despite extensive investigation of risk factors, it is reported that none is found in about half of women diagnosed with gestational diabetes. The second half of pregnancy per se is considered a diabetogenic state for physiological reasons. During pregnancy, the fetus must be nourished continuously despite the intermittent feeding of the mother, achieved through the fetal-placental-maternal unit being under the control of placental hormonal secretions that promote maternal insulin resistance. Insulin resistance increases throughout pregnancy and is well established by the 24th week. Maternal hyperglycaemia occurs in circumstances of the failure to increase insulin secretion or additional insulin resistance in otherwise predisposed women.

Consequences of hyperglycaemia in pregnancy

Overview

Hyperglycaemia in pregnancy is associated with increased risk of adverse events affecting the mother, compromising the fetus, complicating the delivery process, and increasing morbidity in newborn infants. We now know it has long-term consequences in the offspring (see Table 9.1).

In the case of diabetes in pregnancy, as hyperglycaemia may have been present at conception and embryogenesis increases the vulnerability and risk of complications. Hyperglycaemia during the critical period of organogenesis may lead to a high risk of spontaneous abortions and congenital anomalies. Microvascular complications

13 Metzger et al., 2008.

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of diabetes such as retinopathy or nephropathy, are also more likely in the mother and tend to exacerbate during pregnancy.

Gestational diabetes more commonly implies relatively milder hyperglycaemia compared to diabetes in pregnancy but is nonetheless associated with poor pregnancy outcome in the absence of appropriate management, and future risk of diabetes and cardiovascular disease.

Gestational diabetes is associated with a higher incidence of maternal morbidity, including caesarean deliveries, shoulder dystocia, birth trauma, hypertensive disorders of pregnancy (including preeclampsia) and subsequent development of type 2 diabetes. Perinatal and neonatal morbidities are also increased; the latter include macrosomia, birth injury, hypoglycaemia, polycythaemia and hyperbilirubinemia. Long-term sequelae in offspring with in utero exposure to maternal hyperglycaemia include higher risks of obesity, impaired glucose metabolism and diabetes later in life.

Relevance to DOHaD

Growth and development of the human conceptus occur within the metabolic milieu provided by the mother and the fetus and are dependent on the transfer of nutrients from the maternal circulation via the placenta. Early studies demonstrated that newborn infants of diabetic mothers suffered from hypoglycaemia.[14] It was hypothesised that this was due to hyperinsulinism as a consequence of the increased transplacental transfer of sugar, and later research confirmed the presence of hyperplasia of the insulin-producing β cells in infants of diabetic mothers. Ultimately, hyperplasia could have consequences in later life; in animal experiments, Aerts and Van Assche showed that modifications in the endocrine pancreas during intrauterine life cause persistent changes in later adult life (second generation), which though not perceptible in basal conditions, become apparent in situations stressing the β cell activity, such as pregnancy.[15] During pregnancy in the second-generation rats, increased non-fasting blood glucose and no adaptation of the β cells is seen. This inadequate adaptation to pregnancy causes changes in the fetal endocrine pancreas of third-generation fetuses, thereby suggesting a transgenerational transmission of risk. It is now evident that an abnormal intrauterine environment has consequences in later life mediated through

14 Jacobsen, B.B., Nielsen, F., Pedersen, V.F. & Kildeberg, P. 1988. Residual β cell function in transient neonatal diabetes mellitus (TNDM). *Pediatric Research*, 23:115. [https://doi.org/10.1203/00006450-198801000-00083].

15 Aerts, L. & Van Assche, F.A. 2006. Animal evidence for the transgenerational development of diabetes mellitus. *The International Journal of Biochemistry & Cell Biology*, 38(5-6):894-903. [https://doi.org/10.1016/j.biocel.2005.07.006].

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epigenetic changes and is known as developmental programming. So, it can be concluded that fetal development in an abnormal intrauterine milieu can induce alterations in fetal metabolism, with lasting consequences for the glucose tolerance of the offspring in adult life.[16] The most marked effects being the development of gestational diabetes and with it the transmitting of a diabetogenic tendency to the next generation.

Table 9.1 Adverse events associated with hyperglycaemia in pregnancy.

Maternal and Fetal morbidity associated with gestational diabetes (adapted from the International Federation of Obstetrics and Gynaecology)
Maternal
▪ Pre-and Early Pregnancy
– Spontaneous abortions
▪ During Pregnancy
– Preeclampsia
– Gestational hypertension
– Excessive fetal growth (macrosomia, low gestational age)
– Hydramnios
– Urinary tract infections
– Preterm labour
– Traumatic labour
– Shoulder dystocia
– Instrumental delivery
– Caesarean delivery
– Post-operative/postpartum infection
– Post-operative/postpartum haemorrhage
– Thromboembolism
– Maternal mortality
▪ Puerperium
– Failure to initiate &/or maintain breastfeeding
– Infection
▪ Long-Term Post-Partum
– Weight retention
– Gestational diabetes in a subsequent pregnancy
– Future overt diabetes
– Future cardiovascular disease
Fetal/Neonatal

16 Fetita, L.S., Sobngwi, E., Serradas, P., Calvo, F. & Gautier, J.F. 2006. Consequences of fetal exposure to maternal diabetes in offspring. *The Journal of Clinical Endocrinology and Metabolism*, 91(10):3718-3724. [https://doi.org/10.1210/jc.2006-0624].

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Maternal and Fetal morbidity associated with gestational diabetes (adapted from the International Federation of Obstetrics and Gynaecology)	
–	Stillbirth
–	Neonatal death
–	Non-chromosomal congenital malformations
–	Respiratory distress syndrome
–	Cardiomyopathy
–	Neonatal hypoglycaemia
–	Neonatal polycythaemia
–	Neonatal hyperbilirubinemia
–	Neonatal hypocalcaemia
–	Erb's palsy (as a consequence of birth injury)
DOHaD	
–	Increased predictors and risk of diabetes, obesity, and hypertension in offspring at adult age

An increasing body of evidence supports the hypothesis that the abnormal metabolic environment of the mother with diabetes mellitus may affect specific developing fetal tissues, organs and control systems that will eventually lead to permanent long-term functional implications in adult life. The fetal tissues most likely to be affected are neural cells, adipocytes, muscle cells and pancreatic β cells. Freinkel & Metzger (1979) introduced the concept of pregnancy as a 'tissue culture experiment', in which the placenta and the fetus develop in an 'incubating medium' totally derived from maternal fuels. All these fuels traverse the placenta from the maternal compartment either with (e.g. glucose, lipids) or against (e.g. amino acids) concentration gradients and thus contribute to the fetal milieu. Since these constituents are regulated in part by maternal insulin, disturbances in its supply or actions influence the entire nutritional content to which the fetus is exposed; maternal hyperglycaemia leads to fetal hyperglycaemia and eventually to fetal hyperinsulinemia. According to Freinkel & Metzger (1979)'s hypothesis, the abnormal mixture of metabolites from the mother gains access to the developing fetus in utero, modifying the phenotypic expression in newly-formed cells, in turn determining permanent, short- and long-term effects in the offspring.[17] Depending upon the timing of (embryonic-fetal) exposure to the aberrant fuel mixture, different events may develop. Early in the first trimester, intrauterine growth restriction and organ malformation, described by Freinkel & Metzger (1979) as

17 Freinkel, N. & Metzger, B.E. 1979. Pregnancy as a tissue culture experience: the critical implications of maternal metabolism for fetal development. *Ciba Foundation Symposium 63: Pregnancy Metabolism, Diabetes and the Fetus*, (63):3-28. [https://doi.org/10.1002/9780470720462.ch2].

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'fuel-mediated teratogenesis' may occur.[18] During the second trimester, at the time of brain development and differentiation, behavioural, intellectual or psychological damage may occur. During the third trimester, abnormal proliferation of fetal adipocytes and muscle cells, together with hyperplasia of pancreatic β cells and neuroendocrine cells may be responsible for the development of obesity, hypertension and type 2 diabetes later in life.

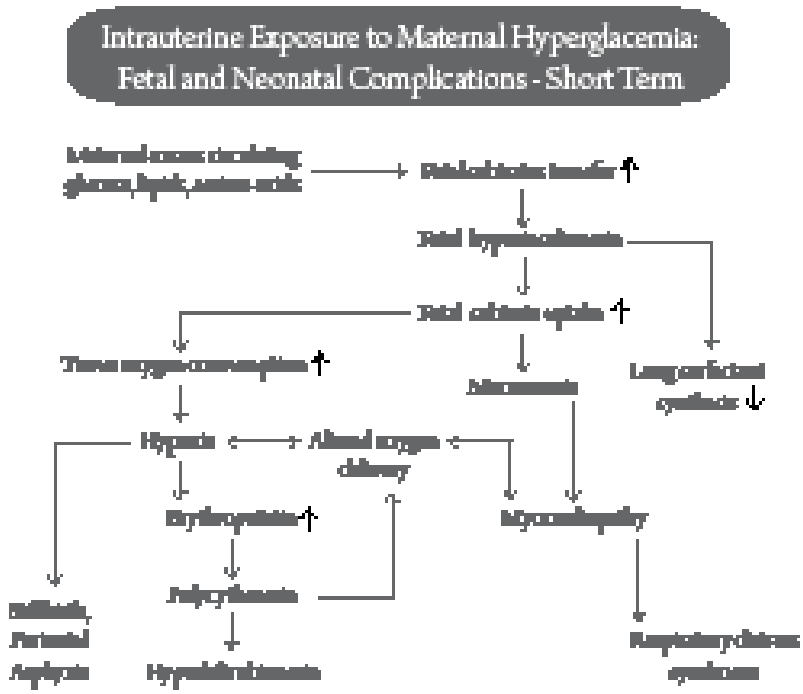

Figure 9.2 Schematic of the fetal and neonatal effects of intrauterine exposure to maternal hyperglycaemia.

Implications for diagnosis

Historical perspective

After decades of uncertainty about the diagnostic criteria of hyperglycaemia in pregnancy, there is an emerging consensus following extensive large studies of outcomes around International Association of Diabetes and Pregnancy Study Group-derived criteria as presented by the WHO in 2013. It is recommended to use a two-hour 75g oral glucose tolerance test with fasting, one-hour and two-hour

18 Freinkel & Metzger, 1979.

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criteria as shown in Table 9.1. There is, however, a lack of consensus across the world for the best screening strategy, whether a universal one-step, a two-step or a risk factor-based screening approach should be used.[19]

African perspective

Recent studies on the prevalence and risk factors of gestational diabetes in an African setting include those by Mwanri, Kinabo, Ramaiya and Feskens (2015); Macaulay, Dunger and Norris (2014); and OlagbujI and colleagues (Atiba, Olofinbiyi, Akintayo, Awoleke, Ade-Ojo and Fasubaa and the Gestational Diabetes Study Group-Nigeria, 2015).[20] Mwanri et al. reported a PubMed-Medline based systematic review of studies published up to June 2014. The 22 studies identified were from Western (n=11), Southern (n=5), Eastern (n=4) and Central (n=2) Africa.[21]

Diagnostic criteria for gestational diabetes varied widely between these studies. Using a 50g glucose challenge test and WHO 1999 criteria, the prevalence of gestational diabetes ranged from 1.5 to three per cent and one to 13.9 per cent, respectively. None of the included studies used criteria from the International Association of Diabetes and Pregnancy Study Group 2010 or the National Institute

19 Atun, R., Davies, J.I., Gale, E.A., Bärnighausen, T., Beran, D., Kengne, A.P., Levitt, N.S., Mangugu, F.W., Nyirenda, M.J., Ogle, G.D. & Ramaiya, K., Sewankambo, N.K., Sobngwi, E., Tesfaye, S., Yudkin, J.S., Basu, S., Bommer, C., Heesemann, E., Manne-Goehler, J., Postolovska, I., Sagalova, V., Vollmer, S., Abbas, Z.G., Ammon, B., Angamo, M.T., Annamreddi, A., Awasthi, A., Besançon, S., Bhadriraju, S., Binagwaho, A., Burgess, P.I., Burton, M.J., Chai, J., Chilunga, F.P., Chipendo, P., Conn, A., Joel, D.R., Eagan, A.W., Gishoma, C., Ho, J., Jong, S., Kakarmath, S.S., Khan, Y., Kharel, R., Kyle, M.A., Lee, S.C., Lichtman, A., Malm, C.P., Mbaye, M.N., Muhimpundu, M.A., Mwagomba, B.M., Mwangi, K.J., Nair, M., Niyonsenga, S.P., Njuguna, B., Okafor, O.L.O., Okunade, O., Park, P.H., Pastakia, S.D., Pekny, C., Reja, A., Rotimi, C.N., Rwunganira, S., Sando, D., Sarriera, G., Sharma, A., Sidibe, A., Siraj, E.S., Syed, A.S., Van Acker, K. & Werfalli, M. 2017. Diabetes in sub-Saharan Africa: from clinical care to health policy. *The Lancet Diabetes & Endocrinology*, 5(8):622-667. [https://doi.org/10.1016/S2213-8587(17)30181-X].

20 Macaulay, S., Dunger, D.B. & Norris, S.A. 2014. Gestational diabetes mellitus in Africa: a systematic review. *PLoS One*, 9:e97871. [https://doi.org/10.1371/journal.one.0097871]; Olagbuji, B.N., Atiba, A.S., Olofinbiyi, B.A., Akintayo, A.A., Awoleke, J.O., Ade-Ojo, I.P. & Fasubaa, O.B. & Gestational Diabetes Study Group-Nigeria. 2015. Prevalence of and risk factors for gestational diabetes using 1999, 2013 WHO and IADPSG criteria upon implementation of a universal one-step screening and diagnostic strategy in a sub-Saharan African population. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 189:27-32. [https://doi.org/10.1016/j.ejogrb.2015.02.030].

21 Mwanri et al., 2015.

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for Health and Clinical Excellence 2015. Overweight or obesity, family history of diabetes, macrosomia or age older than 30 years were the main risk factors of gestational diabetes. Macaulay et al. reported the prevalence of gestational diabetes (estimate: 9.3 per cent) using criteria of the WHO or the American Diabetes Association 2012, while Olagbuji et al. used criteria of the WHO 1999, the WHO 2013, the modified International Association of Diabetes and Pregnancy Study Group and the International Association of Diabetes and Pregnancy Study Group, and reported prevalence rates of 3.8 per cent, 8.1 per cent, 7.5 per cent and 8.6 per cent.[22] Glycosuria was the only correlate of gestational diabetes based on criteria of the WHO 2013 and the International Association of Diabetes and Pregnancy Study Group.

For the first time in an African population, we have explored the diagnostic utility of fasting plasma glucose or random blood glucose alone and the added value of 50g glucose challenge test and the performance of the guidelines for gestational diabetes screening of the WHO 1999, the International Association of Diabetes and Pregnancy Study Group 2010 and the National Institute for Health and Clinical Excellence 2015.

We conducted a cross-sectional study among pregnant women attending antenatal clinics in two major cities in Cameroon. We enrolled consenting pregnant women who attended antenatal care at the participating health facilities, on a consecutive basis until reaching a target sample of 1 000. Pregnant women at 24-28 weeks of gestation were eligible. We excluded women with known diabetes based on medical records. Overall, each consenting participant underwent a risk factor assessment, a random blood glucose test, a fasting plasma glucose test, a one-hour 50g glucose challenge test and a two-hour 75g oral glucose tolerance test.

Risk factor assessment

A structured questionnaire was used to record risk factors for gestational diabetes, including age, occupation, education level, parity, history of a previous stillbirth, history of macrosomia (birth weight ≥ 4 000g), physical activity levels, dietary habits, and characteristics of the ongoing pregnancy. Blood pressure was the average from three consecutive measurements in a sitting position after a ten-minute rest using an Omron M4® recorder. Height and weight were measured in light indoor clothing and without shoes. The body mass index was calculated in kg/m^2. Overweight was defined as having a body mass index of ≥ $25kg/m^2$ and obesity as ≥ $30kg/m^2$.

22 Macaulay, Dunger & Norris, 2014; Olagbuji et al., 2015.

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Testing for gestational diabetes

The women underwent biochemical testing for gestational diabetes on two different occasions. At the first visit, a random plasma glucose test and a one-hour post load 50g glucose challenge test were conducted. At the second visit within one week of the first one, participants underwent testing (after an eight to 12-hour overnight fast) including fasting plasma glucose test, and a 75g oral glucose tolerance test with an assessment of blood glucose at 30, and 120 minutes after a glucose load.

Diagnostic criteria for gestational diabetes

Gestational diabetes was defined by applying three sets of criteria:

- The WHO's definition (1999) as either fasting plasma glucose ≥ 7mmol/L or two-hour post a 75g oral glucose tolerance test, plasma glucose (two-hour PG) ≥ 7.8mmol/L;[23]
- An approximation of the International Association of Diabetes and Pregnancy Study Group-criteria as either fasting plasma glucose ≥ 5.1 mmol/L or two-hour PG ≥ 8.5mmol/L;[24] and
- The National Institute for Health and Clinical Excellence 2015-criteria as fasting plasma glucose ≥ 5.6mmol/L and two-hour PG ≥ 7.8mmol/L.[25]

Implications of the evidence

The prevalence of gestational diabetes in Cameroon varies substantially across diagnostic criteria, from 5.9 per cent by the WHO criteria to 17.7 per cent by the International Association of Diabetes and Pregnancy Study Group-criteria, and 11 per cent by the National Institute for Health and Clinical Excellence-criteria. The presence of gestational diabetes appears to be determined by previous obstetrical

23 World Health Organization (WHO). 1999. *Definition, diagnosis and classification of diabetes mellitus and its complications: Report of a WHO consultation*. Part 1, Diagnosis and classification of diabetes mellitus. [https://apps.who.int/iris/handle/10665/66040] (Accessed 10 September 2019).

24 Metzger, B.E., Gabbe, S.G., Persson, Lowe, L.P., Dyer, A.R., Oats, J.M. & Buchanan, T.A. 2010. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*, 33(3):676-682. [https://doi.org/10.2337/dc09-1848].

25 National Institute for Health and Care Excellence. 2015. *Diabetes in pregnancy: management from preconception to the postnatal period*. NICE guideline [NG3]. [nice.org.uk/guidance/ng3] (Accessed 10 September 2019).

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history and dietary habits. Irrespective of the diagnostic criteria and tests thresholds used, a considerable proportion of women was likely to have severe glucose intolerance and thus was at risk for adverse perinatal outcomes. A conceptually simple diagnostic algorithm with optimal screening yield can be derived based on the performance of various tests in this population and is potentially useful for routine clinical practice in resource-limited settings.

The prevalence of gestational diabetes depends on the chosen screening strategy with the highest prevalence obtained using guidelines of the International Association of Diabetes and Pregnancy Study Group. Irrespective of the diagnostic criteria and test thresholds used, a considerable proportion of women have severe glucose intolerance and are thus at risk for adverse perinatal outcomes. Physical activity, history of stillbirth and alcohol consumption, age, family history of diabetes and macrosomia are significant determinants of gestational diabetes in African populations. Unlike random blood glucose, fasting plasma glucose could be used in a simple screening algorithm to define the segment of pregnant women to be further screened via a 75g oral glucose tolerance test. Where feasible, however, a single step testing strategy using a 75g oral glucose tolerance test is optimal for gestational diabetes screening.

Based on the performance of the screening tests used in our study we propose a simple screening algorithm to optimally identify women with gestational diabetes in sub-Saharan Africa where limited resources are a major deterrent to the implementation of a large-scale and sustainable programme for prevention and management of gestational diabetes-associated complications. The screening algorithm is practical for resource-limited settings and uses fasting glucose measurements, as shown in Figure 9.2. Such a screening strategy, allowing testing of pregnant women first in a fasting state, will facilitate an opportunistic approach to screening and has the potential to maximise the yield of screening in an environment where regular clinic attendance can be an issue.

Comparison with other studies and explanation of our results

A recent study from Nigeria using the WHO criteria to diagnose gestational diabetes reported a prevalence of 8.3 per cent; whereas a previous South-African study found a much lower prevalence (1.5 per cent) with similar criteria in a rural setting.[26]

26 Atun et al., 2017; Mamabolo, R.L., Alberts, M., Levitt, N.S., Delemarre-van de Waal, H.A. & Steyn, N.P. 2007. Prevalence of gestational diabetes mellitus and the effect of weight on measures of insulin secretion and insulin resistance in third-trimester pregnant rural women residing in the Central Region of Limpopo Province, South Africa. *Diabetic Medicine*, 24(3):233-239. [https://doi.org/10.1111/j.1464-5491.2006.02073.x].

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Such differences in gestational diabetes prevalence with previous studies may relate to the fact that these studies have used different screening strategies and diagnostic criteria than those of the screening approach in this study. Elevated rates of gestational diabetes in Cameroonian women may be related to the growing obesity in women in sub-Saharan Africa.[27] In our study, only previous stillbirth and alcohol consumption were associated with the presence of gestational diabetes. There are several possible explanations for the lack of association between traditionally known risk factors and gestational diabetes, which include our relatively small sample size with a low prevalence of some of these risk factors in our sample, or the low awareness of these risk factors in our population. The paradoxical association of increased physical activity from walking with a high prevalence of gestational diabetes may simply be related to chance or the subjective nature of physical activity assessment.

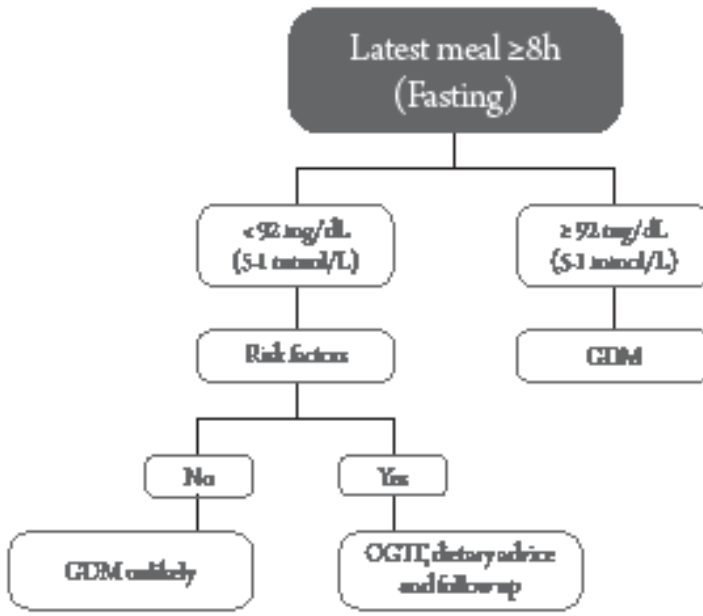

Figure 9.3 Proposed screening algorithm for gestational diabetes in resource-limited settings.

Our estimates of the performance of various screening tests differ from those reported in previous studies.[28] The observed difference is at least partially related

27 Mwanri et al., 2015; Macaulay, Dunger & Norris, 2014.

28 Senanayake, H., Seneviratne, S., Ariyaratne, H. & Wijeratne, S. 2006. Screening for gestational diabetes mellitus in southern Asian women. *Journal of Obstetrics and Gynaecology Research*, 32(3):286-291. [https://doi.org/10.1111/j.1447-

https://doi.org/10.18820/9781928357759/09

to population structure with potential differential gestational diabetes baseline risk, sample size and tests used, as well as cut-offs. Indeed, many previous studies did not include random blood glucose in their assessment, although it is a fast, simple, and relatively inexpensive test. However, its accuracy has been less frequently studied than that of other screening tests, with indications that its performance as a screening test for gestational diabetes may be limited. Nasrat, Johnstone and Hasan (1988) found a sensitivity of 16 per cent and a specificity of 96 per cent using a threshold value of 7mmol/L or 6.4mmol/L if evaluated against two-hour postprandial.[29] Consistent with our findings, Jowett, Samanta and Burden (2017) concluded that random glucose measurement might not be sufficiently sensitive for screening on gestational diabetes as a stand-alone test.[30] Despite these limitations, from a public health perspective, including fasting plasma glucose as an initial test in a stepwise screening for gestational diabetes using a combination of various tests, appear as a promising practical approach for detecting gestational diabetes in under-resourced settings (where universal screening is not always possible). Opportunistic screening with random blood glucose would lead to more gestational diabetes cases diagnosed.

Conclusion

Rapid demographic, sociocultural, and economic transitions are driving increases in the risk and prevalence of diabetes and other non-communicable diseases in sub-Saharan Africa. The impacts of these transitions and their health and economic consequences are evident. In 1990, the leading causes of death in sub-Saharan Africa were HIV/Aids, lower respiratory infections, diarrhoeal diseases, malaria, and vaccine-preventable diseases in children. In more recent years, cardiovascular diseases and their risk factors are replacing infectious diseases as the leading causes of death in this region, and rates of increased cardiovascular risk factors are

0756.2006.00400.x]; Agarwal, M.M., Dhatt, G.S. & Punnose, J. 2006. Gestational diabetes: utility of fasting plasma glucose as a screening test depends on the diagnostic criteria. *Diabetic Medicine*, 23(12):1319-1326. [https://doi.org/10.1111/j.1464-5491.2006.01987.x]; Agarwal, M.M., Dhatt, G.S. & Shah, S.M. 2010. Gestational diabetes mellitus: simplifying the international association of diabetes and pregnancy diagnostic algorithm using fasting plasma glucose. *Diabetes Care*, 33(9):2018-2020. [https://doi.org/10.2337/dc10-0572].

29 Nasrat, A.A., Johnstone, F.D. & Hasan, S.A. 1988. Is random plasma glucose an efficient screening test for abnormal glucose tolerance in pregnancy? *British Journal of Obstetrics and Gynaecology*, 95(9):855-860. [https://doi.org/10.1111/j.1471-0528.1988.tb06569.x].

30 Jowett, N.I., Samanta, A.K. & Burden, A.C. 2017. Screening for diabetes in pregnancy: is a random blood glucose enough? *Diabetic Medicine*, 4(2):160-3. [https://doi.org/10.1111/j.1464-5491.1987.tb00854.x].

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predicted to be higher in sub-Saharan Africa than in other parts of the world. Thus, sub-Saharan Africa, containing a high proportion of the world's least developed countries, will face the multifaceted challenge of dealing with a high burden of infectious diseases and diseases of poverty, while also addressing the increasing burden of cardiovascular disease and its risk factors. At present, many of the health systems in sub-Saharan Africa struggle to cope with infectious diseases. Meeting the goals of the United Nations high-level meeting on non-communicable diseases (to reduce premature mortality from non-communicable diseases by 25 per cent by 2025) and the Sustainable Development Goals (to reduce premature mortality from non-communicable diseases by a third by 2030) requires a coordinated approach within countries, starting with a firm consideration of disease burden, needs, and priorities.[31]

31 Atun et al., 2017.

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